Emerging Infections & Update in STIs

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Infectious Disease

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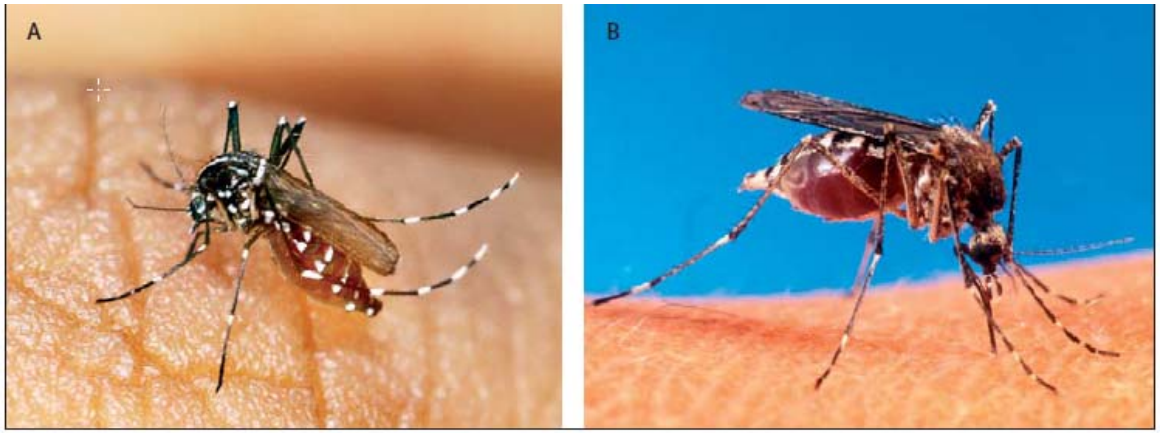


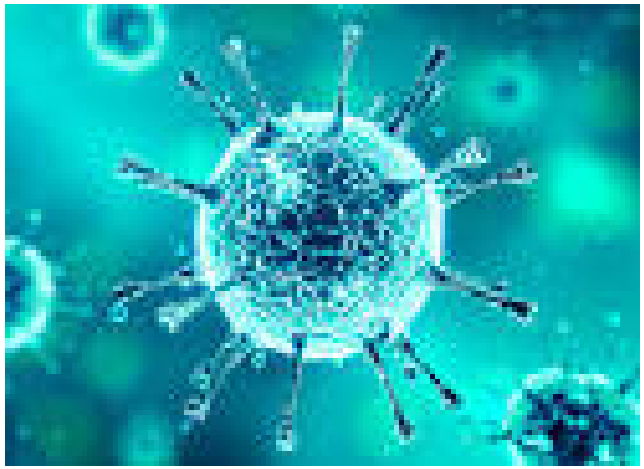
***Figure 1*: Mosquito vectors of chikungunya virus**
(A) Blood-gorged *A albopictus* female feeding on a human host. *A albopictus* is the primary chikungunya virus vector in the current Indian Ocean outbreak. (B) *A aegypti* mosquito. *A aegypti* is the primary chikungunya virus vector in Asian chikungunya outbreaks. Images from United States Department of Agriculture.

Objectives

- Know the evolving epidemiology and risk of chikungunya & *Babesia* infection
- Recognize features of chikungunya infection and babesiosis and methods of diagnosis
- Review evolving diagnostic and treatment strategies for certain STDs

Disclosures: None

Chikungunya Virus



Family Togaviridae

-Alphavirus (29 SS RNA viruses)

Old World: 6 cause human joint dz

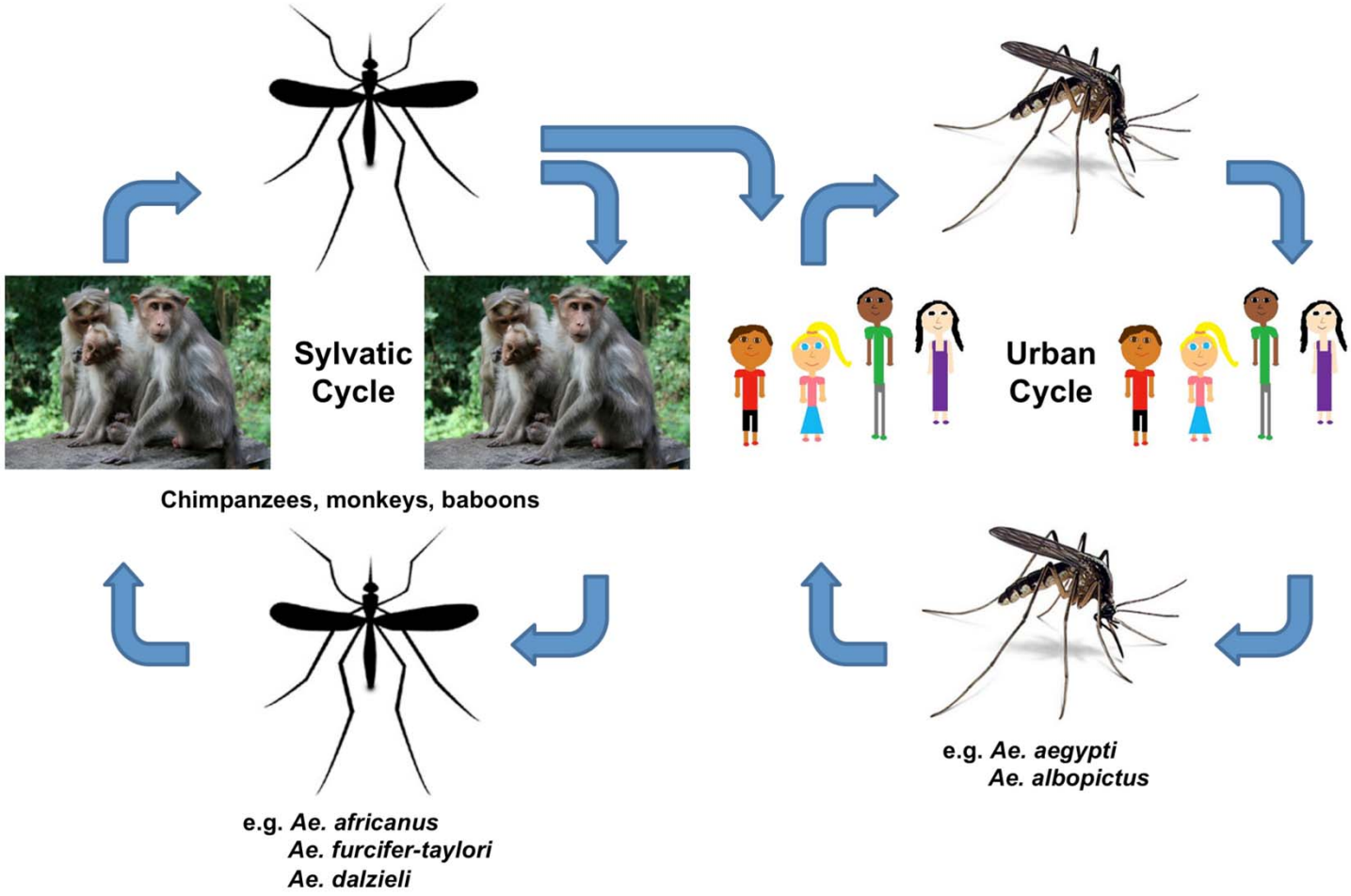
- O'nyong-nyong virus
- Ross River virus
- Mayaro virus
- Semliki virus
- Sindbis virus
- Chikungunya

New World: Encephalitis Viruses (EEEV, VEEV)

Reportable illness

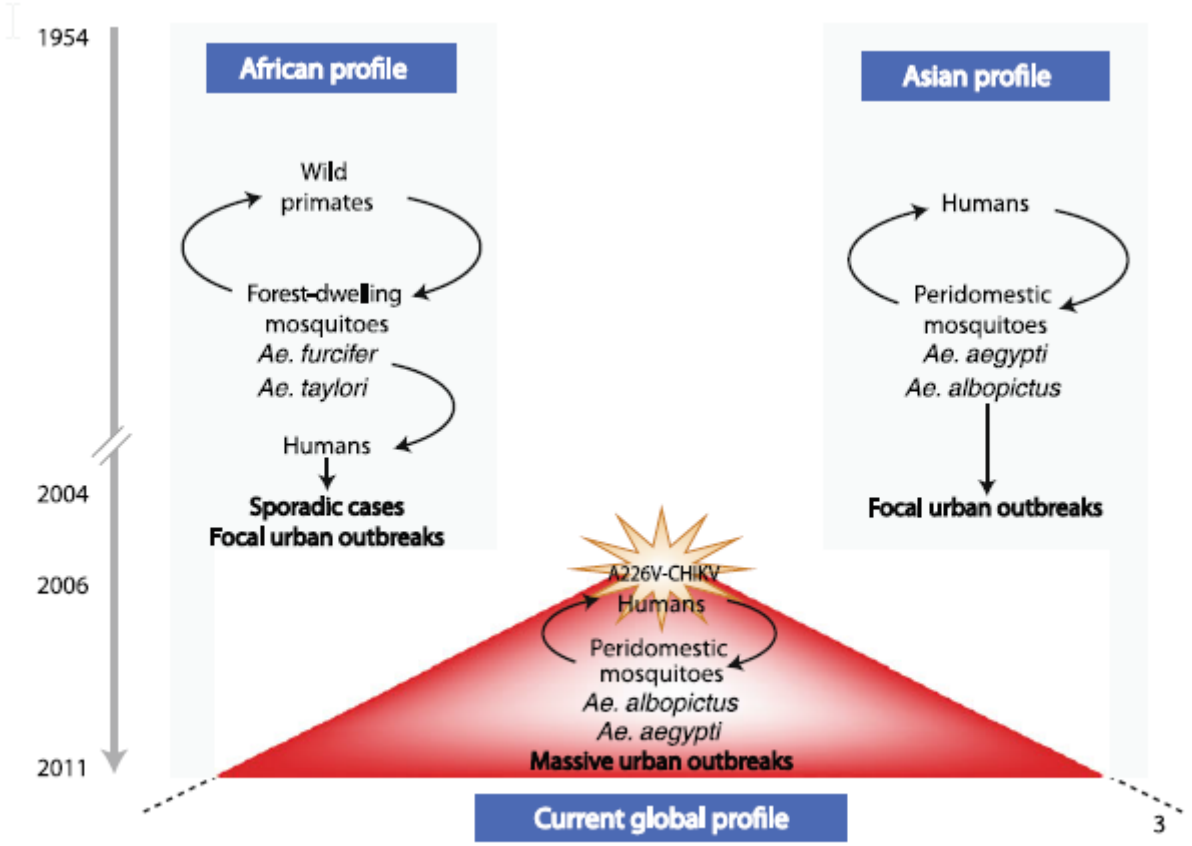
Chikungunya Life Cycle

(Thiboutot PLoSntds 2010 4(4):e623)



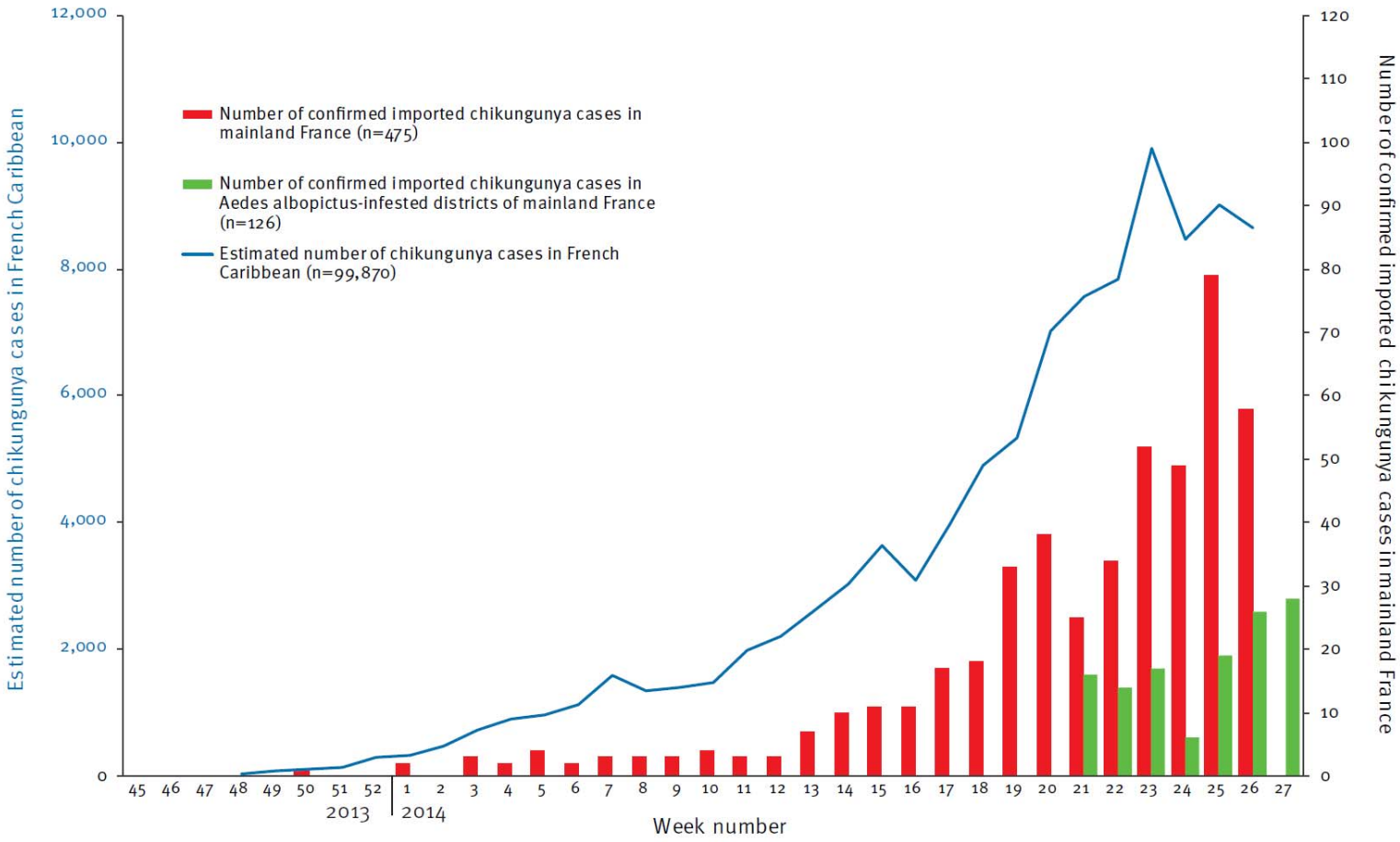
Evolving Profile of Outbreaks

(Simon Curr inf Dis Rep 2011;13:218)



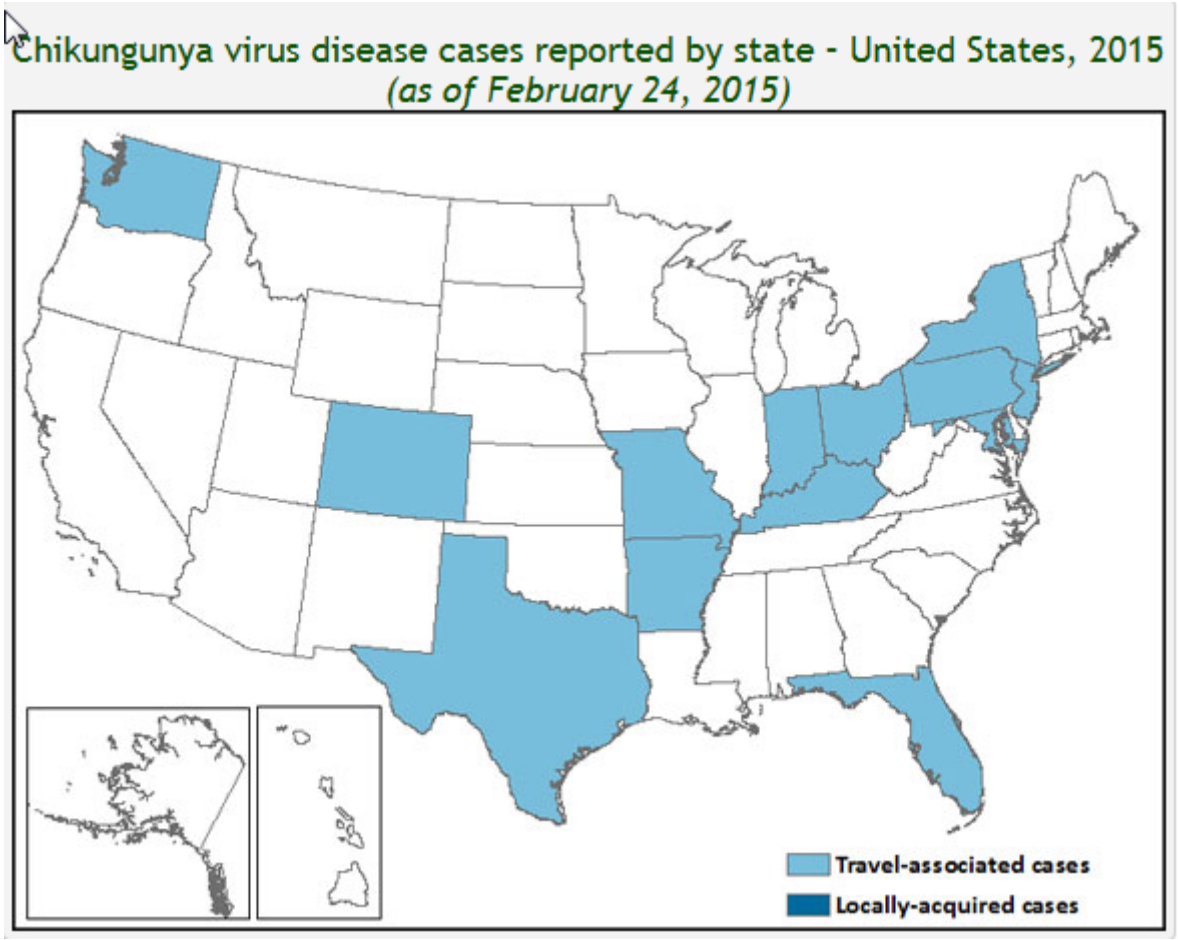
Imported Chikungunya: France 2014

(Paty Euro Surveill 2014;19(28):20856)



U.S. Cases of Chikungunya 2015 (CDC)

43 cases (FL, NY > TX, PA, etc); 45 cases in territories



Aedes vectors in U.S.

Chikungunya: Clinical Illness

- Chikungunya = “that which bends up”

  Makonde (Tanzania)
- High rates of illness if infected (~95%)
- Incubation: 3-7 days
- Acute phase: abrupt fever, severe arthralgia & myalgias, prostration > rash

  High viral load [10(9) - 10(12) copies/ml]
- Chronic phase: Polyarthralgia>arthritis, enthesitis, soft tissue pain & fatigue x weeks to years

Chikungunya: Time Course

(Pialoux Lancet Inf Dis 2007 7:319)

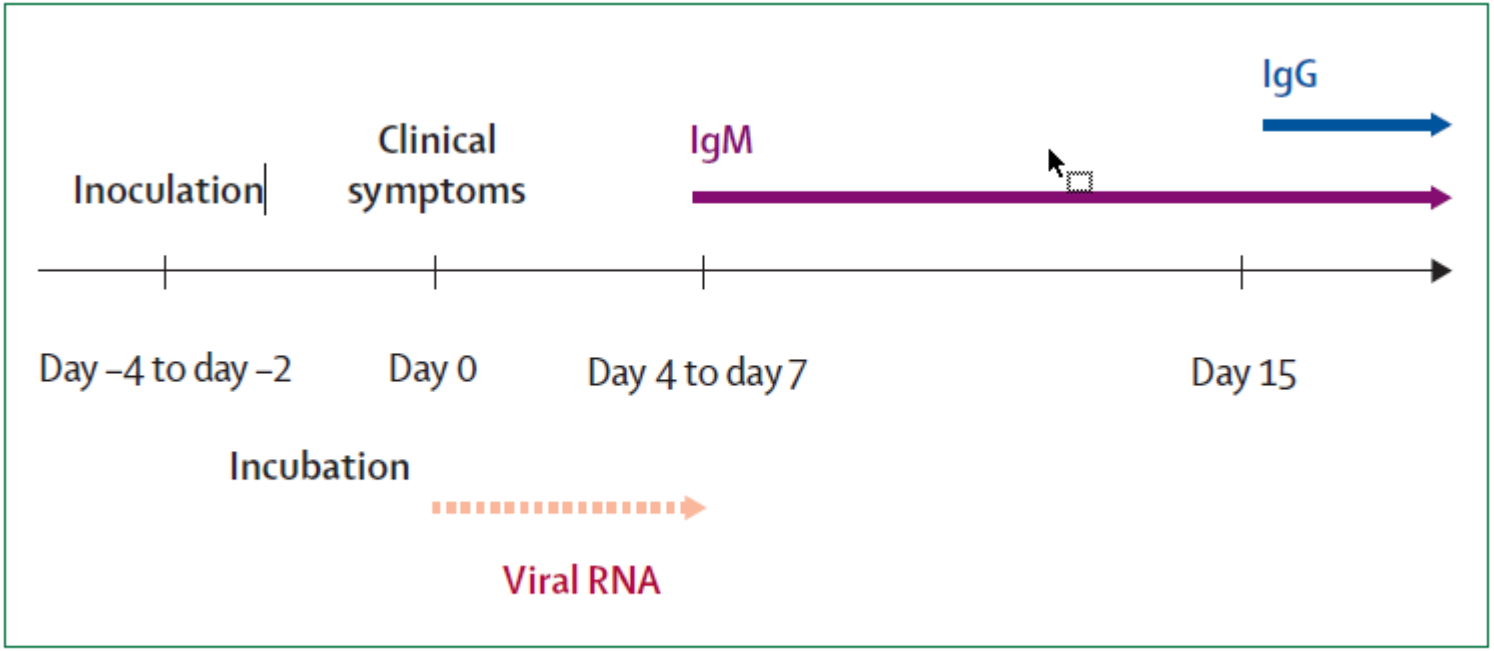


Figure 6: Biological diagnosis of chikungunya

Acute Chikungunya

(Pialoux Lancet Inf Dis 2007;7:319)

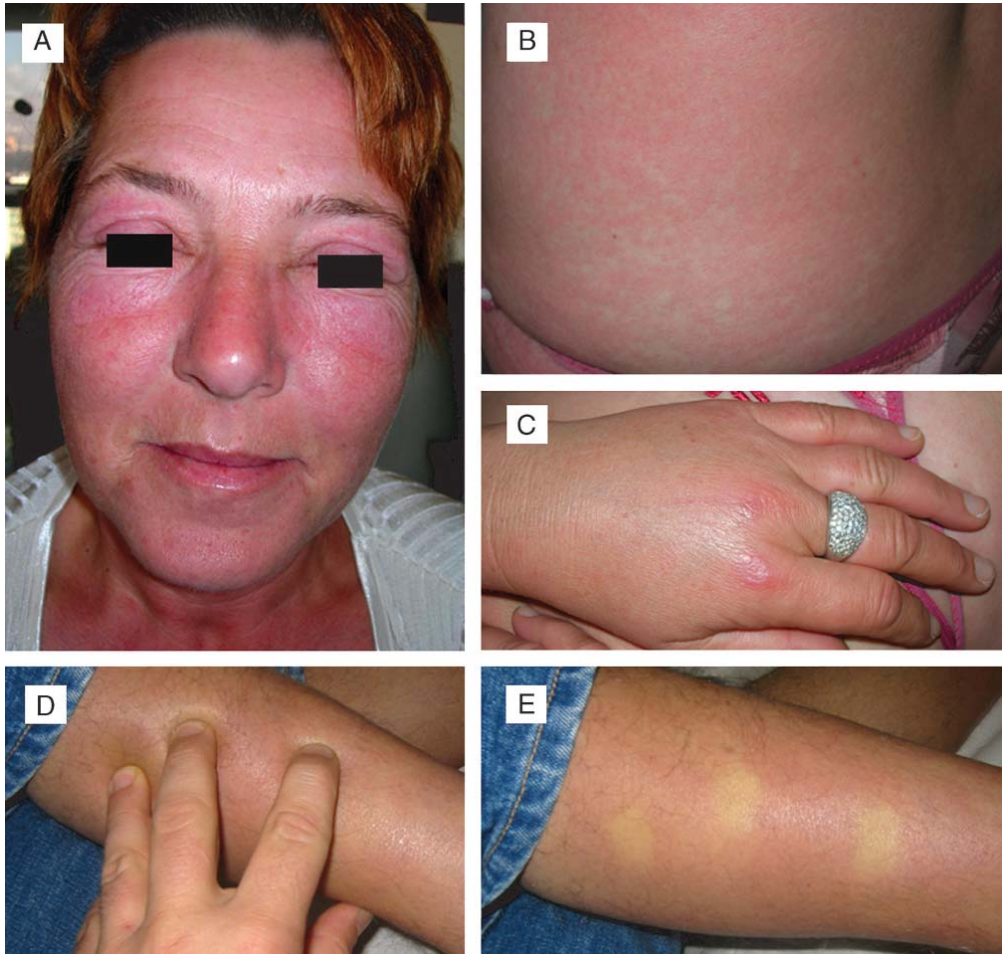
	Malaysia 1998 (%)	Réunion 2005–Feb 2006 (%)
Skin rash	50	39
Myalgia	50	60
Headache, spinal pain	50, 50	70, NR
Arthralgia (all types)	78	100
Large joints	18	NR
Fever	100	100
Number of reported cases	51	504

NR=not reported. Data for Malaysia from Lam and colleagues (2001)[19] and data for Réunion from http://www.invs.sante.fr.

Table: **Frequency of clinical manifestations during the 1998 Malaysian epidemic and the 2005 Réunion epidemic**

Adult Skin Manifestations: Return from Reunion Island

(Simon Medicine 2007; 86(3):123)



Rash of Chikungunya in Children

(Pialoux Lancet Inf Dis 2007 7:319) (Robin Eur J Peds 2010;169:67)

Laboratory Findings: Acute Dz

- Elevated LDH, AST, ALT, GGT
- Elevated CK
- Mild thrombocytopenia
- No or mild leukopenia
- Elevated ESR and CRP in majority

Rare: marked cytopenias

Chikungunya vs Dengue

Epidemiology overlaps

Identical vectors

Dengue: differentiating features

- Lymphadenopathy
- Retro-orbital/ocular pain
- Diaphoresis
- Prominent back pain >> peripheral joint pain
- Absent arthritis/tenosynovitis
- Bleeding more common

Rare/Uncommon Complications

- Severe cytopenias
- Myocarditis
- Meningoencephalitis, GBS, flaccid paralysis
- Mild hemorrhage
- Neonatal infection (if mom viremic near parturition)
- Incidence of severe dz: < 0.02%

  more common w/ older age/co-morbidities

  (Reunion Island: mortality rate est 0.3-1%)

Acute Chikungunya

Diagnosis

- Serology (ELISA)

  IgM (usually present by Day 5-7 of illness) or

  IgG (us by 2 wk; 4x rise b/t acute/convalesc.)

  (caveats: x-reactive Ab, FN w/ cryoglob's, persistent IgM x mos)

- Viral PCR of blood (or vesicle fluid)

  Through Day 7 of illness

- Viral culture: not routinely used (BSL 3)

Treatment: pain medications/NSAIDs; avoid ASA

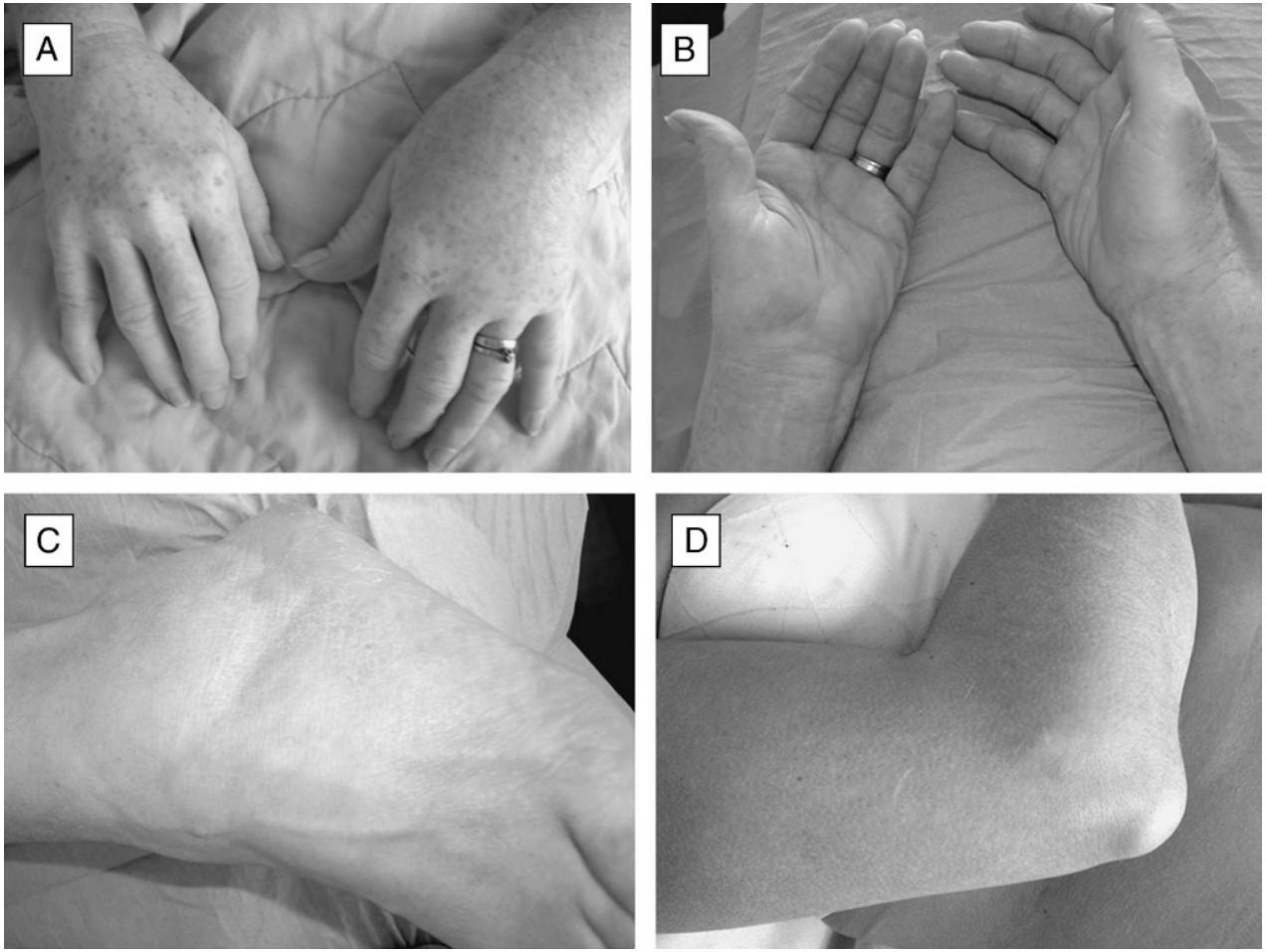
steroids effective but w/ rebound effect

Second Stage of Chikungunya (>10 days)

- Persistent/relapsing arthralgias and stiff joints
- Exacerbation of prior rheumatic conditions
- Tenosynovitis: usually > 2 sites (hypertrophic)
  wrists/hands and ankles
- Transitory vascular disorders (Raynaud syndrome)
  possibly 2nd to mixed cryoglobulins
- Decreased strength
- Ocular: ant uveitis, retinitis, episcleritis, optic neuritis
- Chronic sx's associated with:
  Age > 60 yrs High viral load
  High [TNF-a] and [IL12] (Hoaru)

Joint Manifestations: Return from Reunion Island; > 10 d illness

(Simon Medicine 2007; 86(3):123)



MSK DZ of chronic CHIK (Simon Curr Inf Dis Resp 2011;13:218))

Babesiosis

- Emerging Infection, nationally reportable ’11

  Incr recog/# immunocompr; Changing ecology

- Apicomplexan (malaria, toxo); > 100 spp infect animals

  2nd most-common blood parasite in mammals (<tryps)

- Human infx: U.S.—*B. microti*

  Ixodes scapularis vector; Mice/deer reservoir

  Rare: *B. duncani* (WA/CA) or *B. divergens*-like (KY/MO/WA)

  Risk: Transfusion transmission

nejm babesia

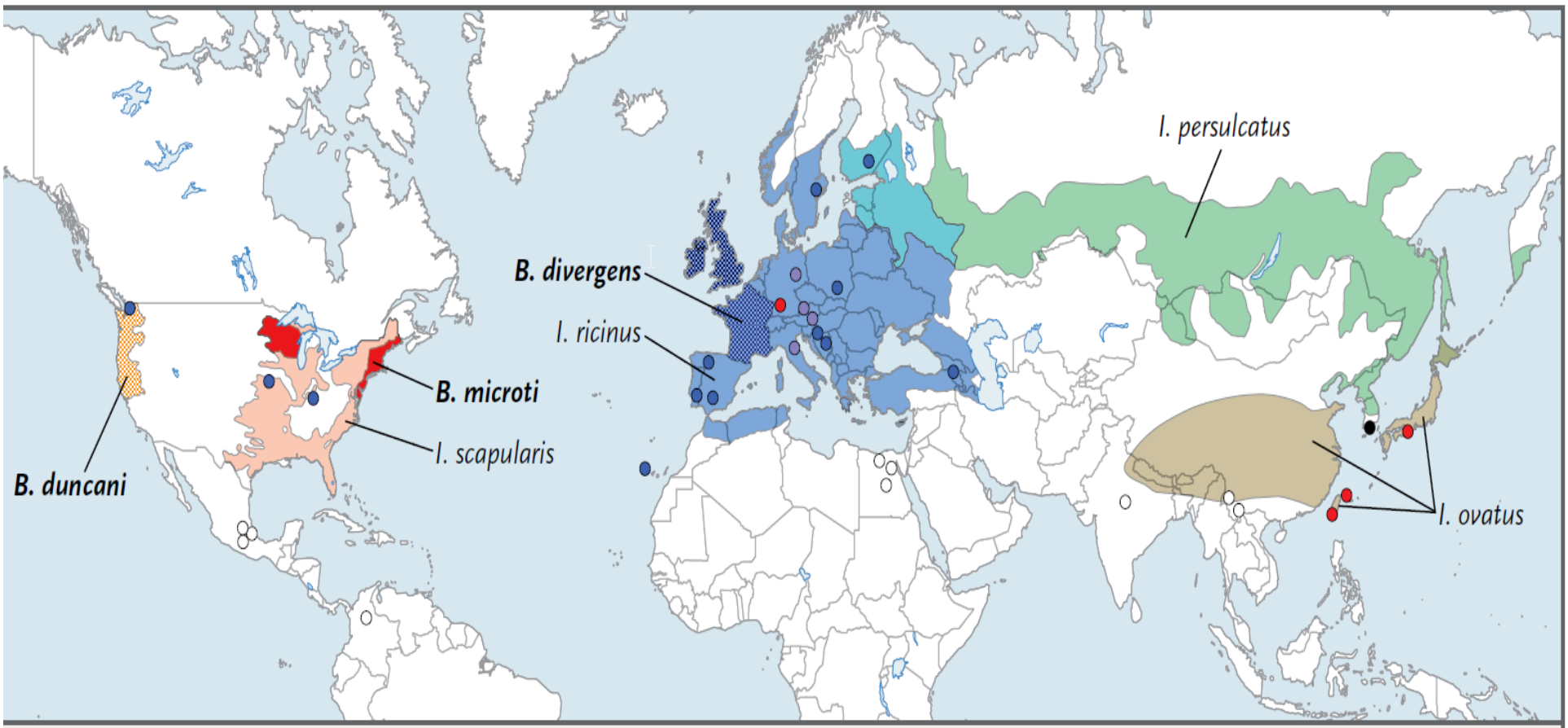
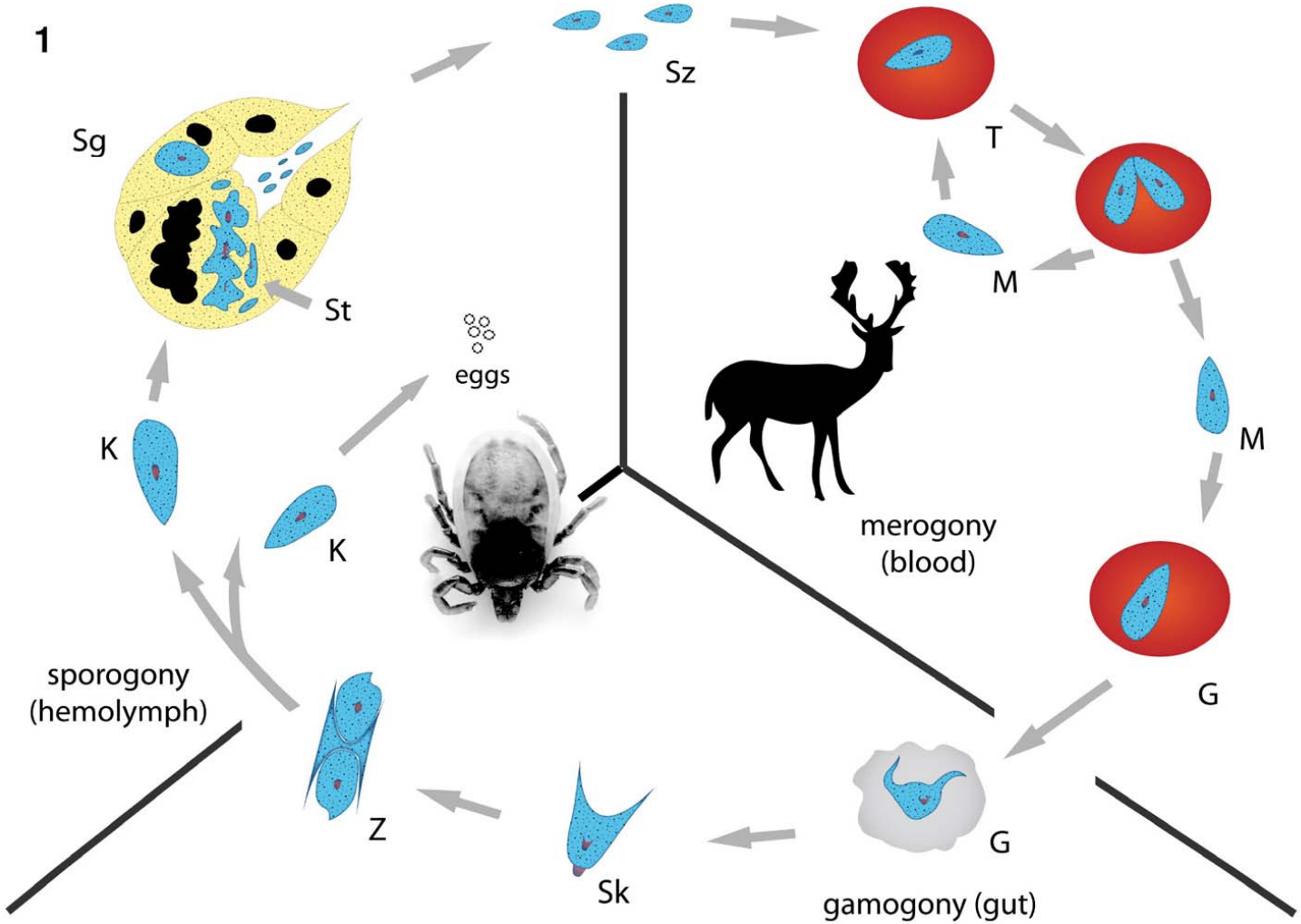


Figure 1. Geographic Areas Where Human Babesiosis and Ixodes Tick Vectors Are Endemic.

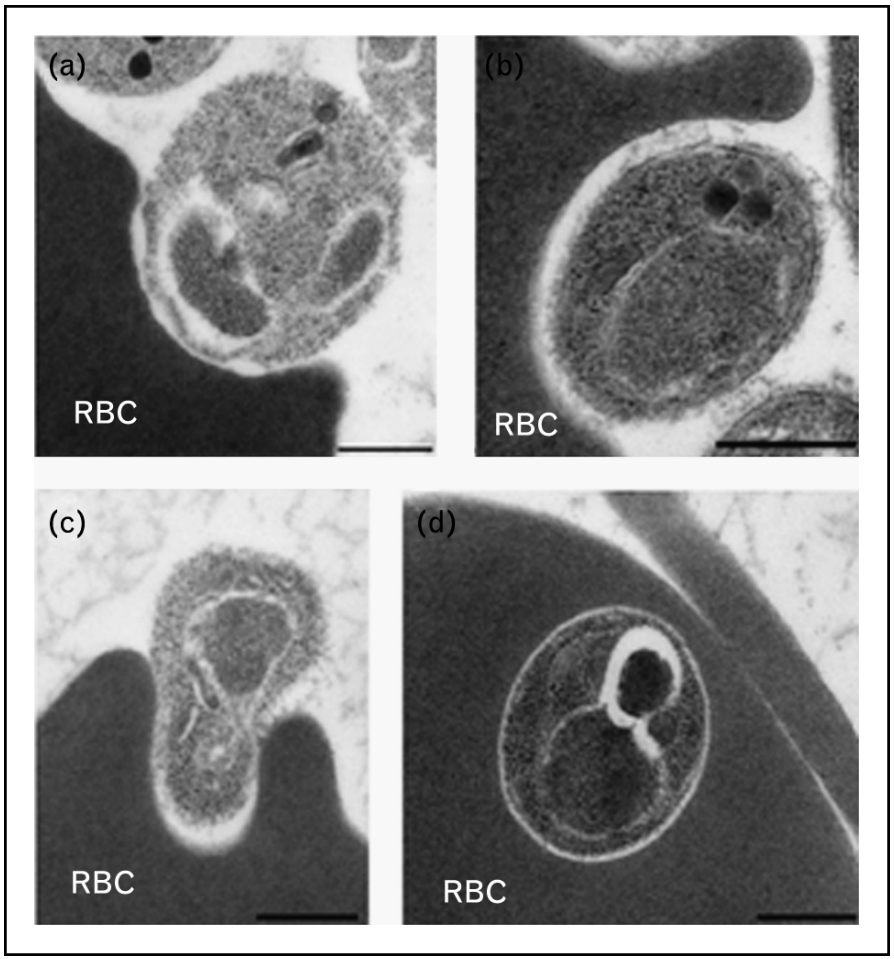
Life Cycle of Babesia

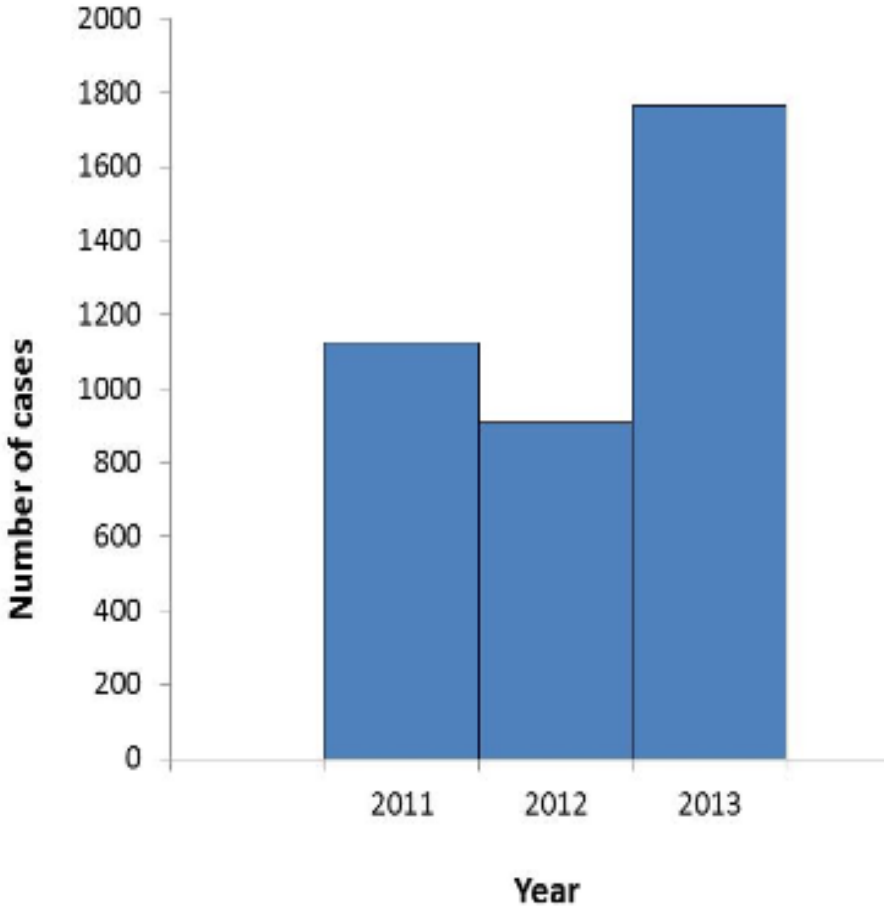
(Hunfeld Int J Parsit 2008 38:1219)



Babesia: Pathogenesis and Burden in U.S.

(Lobo Curr Opin Hematol 2012 12:170)(CDC--graph)





Wide spectrum of clinical severity

Sx's: 1-4 wks after bite; 1-9 wks after PRBCs

-Gradual malaise, then fever/chills/sweat

- Myalgia, cough, arthralgia, nausea >

abd pain, photophobia, depression, conjunctivitis,

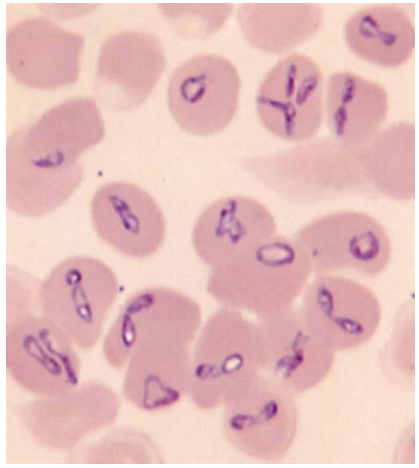
Exam: splenomegaly, OP erythema, jaundice

Labs: low hgb/hapto & plt's; incr retic/LDH

Immune Competence & Babesiosis

Immunocompetent: 25% no sx's

- If sx's: 1-2 wks F/C, fatigue x mos
- A'sx parasitemia x months w/ tx; > 1 yr w/o tx



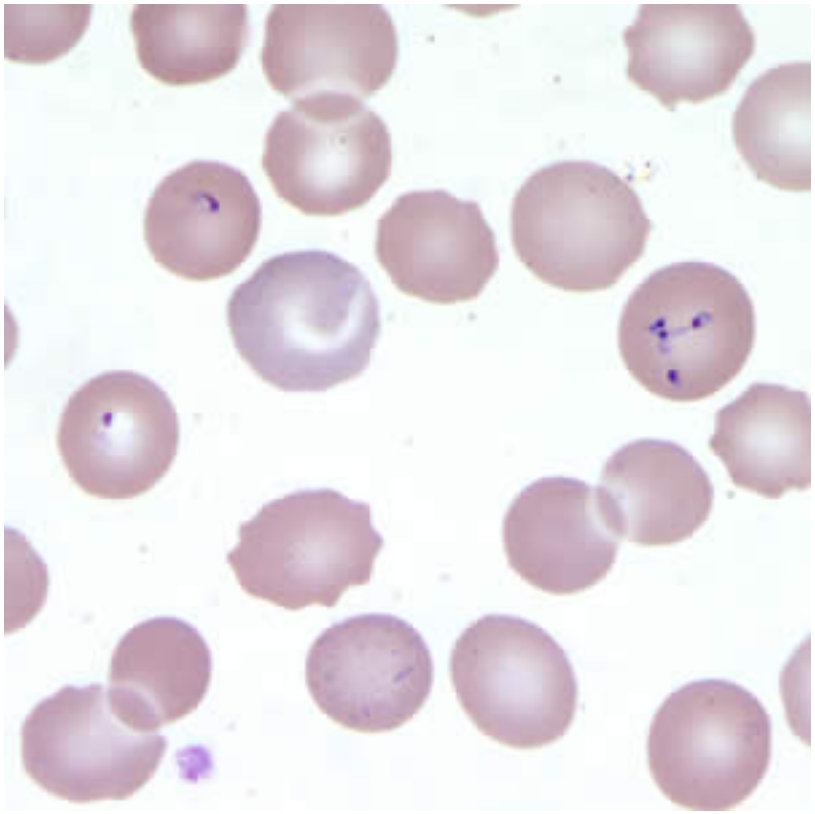
Immunodeficient: can see fulminant dz

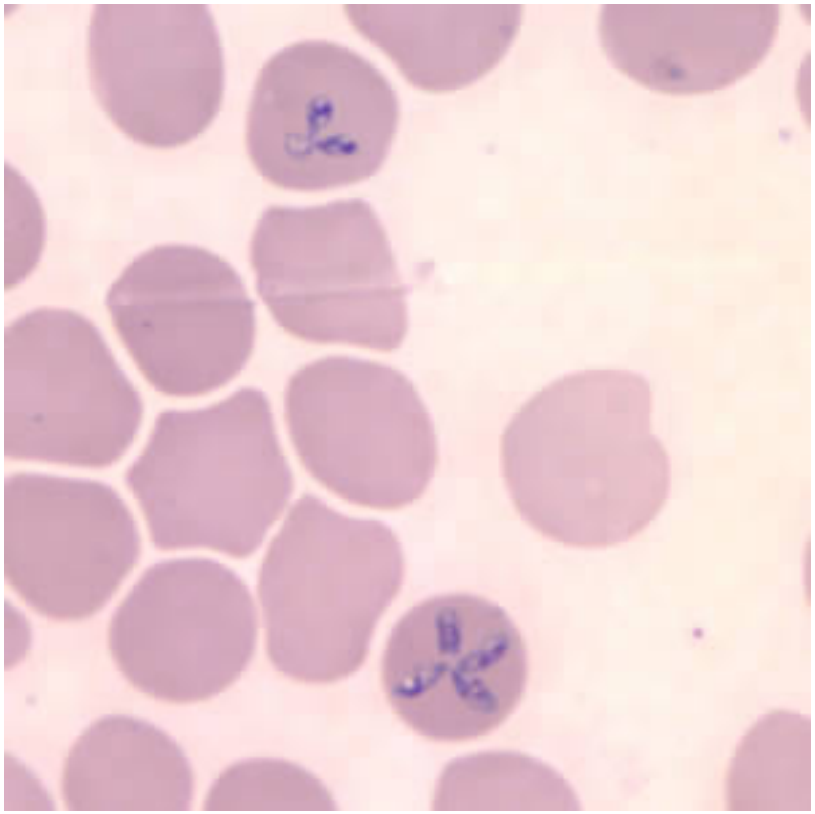
- Splenect, CA, SOT, HIV, SC, a-TNF, X-age
- ARDS, DIC, CHF, coma, liver failure, AKI
- Fatality rate: up to 20% w/ immunosuppression

Diagnosis of Babesiosis

- Consider: any pt w/ febrile illness & residence in/travel to endemic area < 2 mos or blood transfusion < 6 mos
- Strong clinical suspicion required since no classic signs
- Automated blood counter will not detect
- Suspect co-infx w/ Lyme/*Anaplasma* if more severe disease/poor response to tx

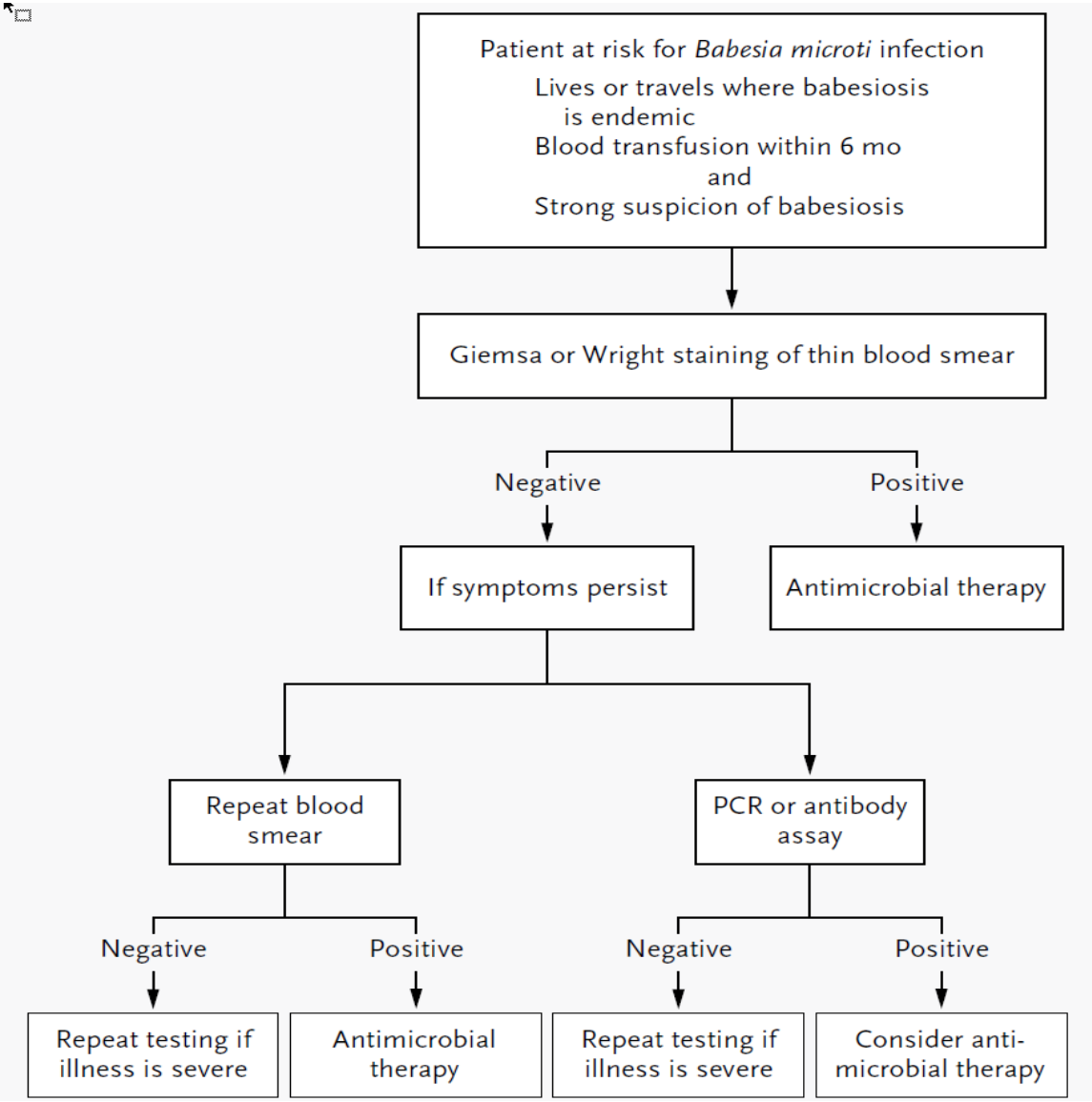
Thin Smears w/ *Babesia microti*





Diagnostic Algorithm

(Vannier nejm 2012;366(25):2397)



Transfusion-transmitted Babesia

-Most common & potentially morbid microbiologic threat of transfusion (Katz '14 Transfus)

-Herwaldt *et al* (Annals Int Med 2011 155(8):509)

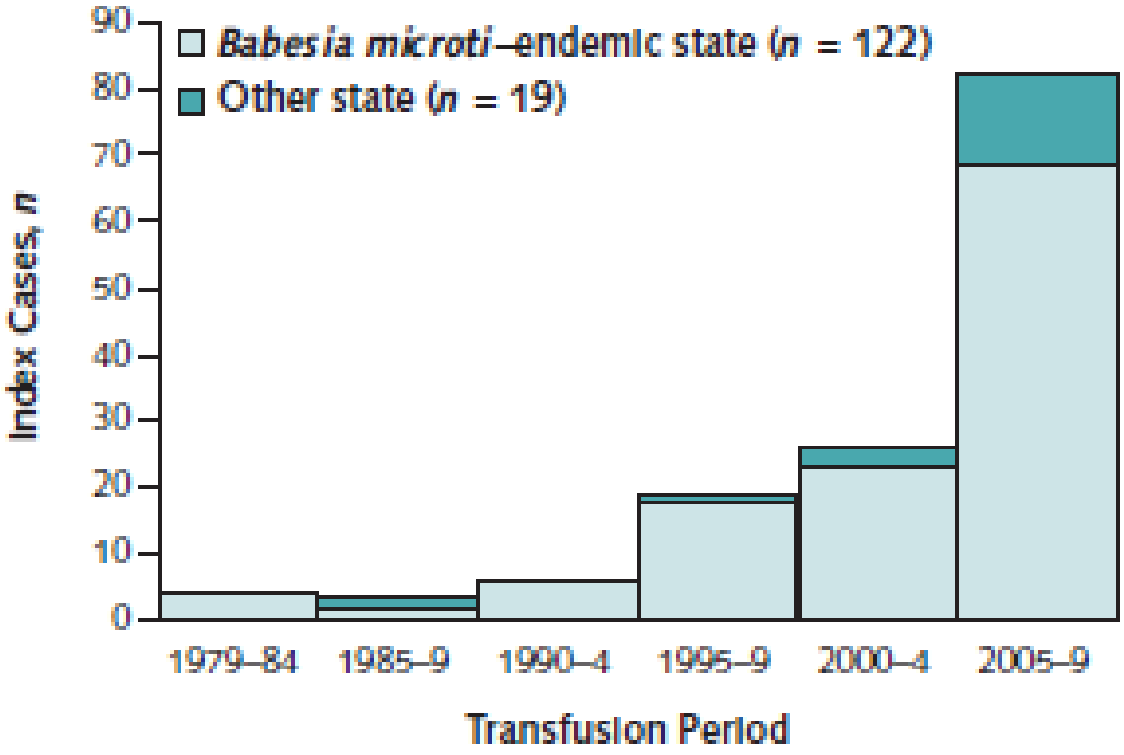
- CDC compiled cases transfused 1979-2009
- Assume under-reporting and missed dx's
- 162 cases; donors implicated for 86%
- PRBCs >>> plts; 18% all-cause mortality
- All seasons; Many pts at risk of severe dz
- 19 states, 87% in 7 main endemic states

-Tonnetti ('09 Transfusion): 5/18 fatal cases

Transfusion-Transmitted Babesia Timeline

(Herwaldt Annals Int Med 2011 155(8):509)

Figure 2. **Distribution of U.S. transfusion-associated *Babesia microti* index cases, 1979–2009.**

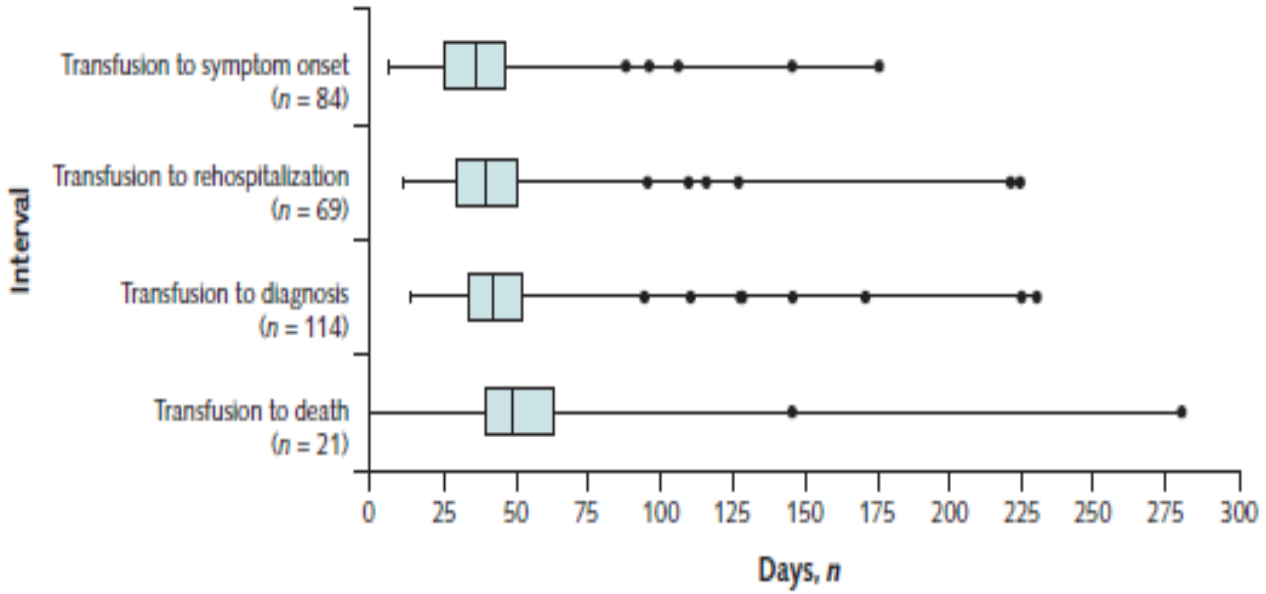


Cases, *n*

Transfusion-Transmitted Babesia

(Herwaldt Annals Int Med 2011 155(8):509)

Figure 3. **Box-and-whisker plots of the distributions of time from transfusion to various events for U.S. transfusion-associated *Babesia microti* index cases, 1979–2009.**



Blood Supply & Babesia

- No FDA-approved screening test
- Regional risk: broad policy more challenging
- Current query of hx of babesiosis
- Assessed Serology or PCR:
- Unfavorable cost/benefit ratio in safety budgets

Treatment of Babesiosis (Table: Vannier nejm)

Table 1. Antimicrobial Treatment of Human Babesiosis.*

Treatment	Dose
Atovaquone and azithromycin†	
Atovaquone	Adult, 750 mg; pediatric, 20 mg/kg (maximum, 750 mg/dose) every 12 hr
Azithromycin	Adult, 500 mg on day 1 and 250 mg on subsequent days; pediatric, 10 mg/kg (maximum, 500 mg/dose) on day 1 and 5 mg/kg (maximum, 250 mg/dose) on subsequent days
Clindamycin and quinine	
Clindamycin	
Oral	Adult, 600 mg every 8 hr; pediatric, 7–10 mg/kg (maximum, 600 mg/dose) every 6–8 hr
Intravenous	Adult, 300–600 mg every 6 hr; pediatric, 7–10 mg/kg (maximum, 600 mg/dose) every 6–8 hr
Quinine	Adult, 650 mg every 6–8 hr; pediatric, 8 mg/kg (maximum, 650 mg/dose) every 8 hr

No sx's & immunocompetent: Tx if continued infx @ 3 months

Wks of tx depends on immunocompetence/relapse (1-2 wks vs 4+ wks)

High parasitemia: adjunctive RBC exchange

Poor tolerance w/ quinine regimen (cinchonism, N/V)

Monitor parasitemia load if severely ill until < 5%

Part 3: Update of STIs

- Recommended screening tests for populations
- Evolving aspects of NGU
- Evolving aspects of Tx of Chlamydia, Gonorrhea

Sexually Active MSM:
Annual Screening Tests & Other Care

- HIV if pt/partner w/ > 1 partner
- Syphilis serology
- Urethral** Chlamydia/Gonorrhea (urine NAAT)
- Rectal** Chlamydia/Gonorrhea (rectal swab for NAAT)
- Pharyngeal** Gonorrhea (NAAT preferred)

(STI screen q 3-6 months if ongoing multiple partners)

- Hep B sAg
- If HIV (+): Hep C Ab (Viral load if CD4<200 & incr ALT)

(HPV vaccine if ≤ 26 yrs; Hep A/B vaccines if nonimmune)

(**based on sexual practices/sites of exposure)

(NAAT=nucleic acid amplification test)

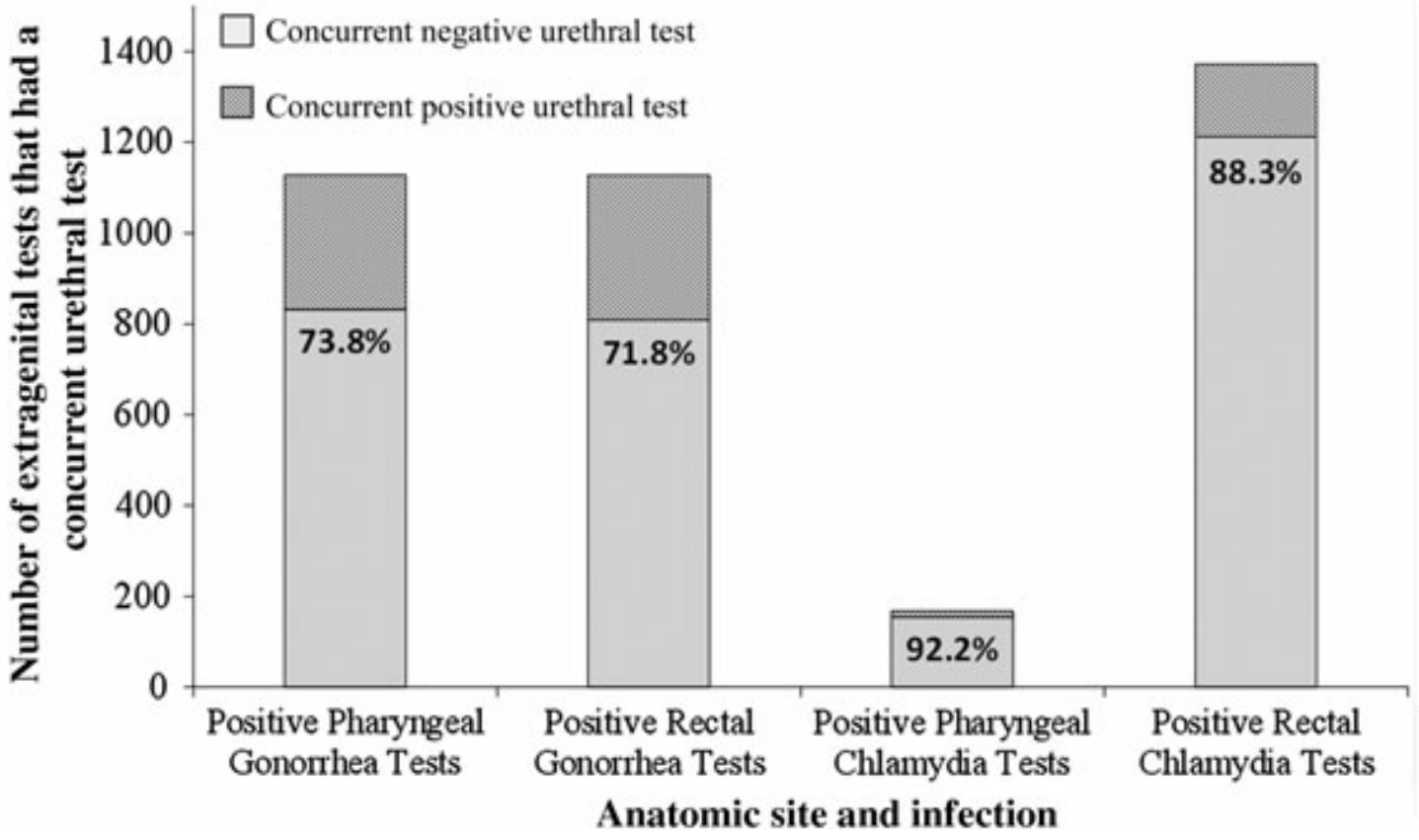
Extragenital GC/CT Infection in MSM

MSM @ STD Clinic (Patton Clin Inf Dis 2014;58:1564)

GC: 8% pharyngeal, 10% rectal (at recent visit or prior year)

CT: 32% pharyngeal, 46% rectal

Graph: proportion of positive GC/CT tests w/ neg urethral tests



CT Screening and Women

(Gratrix Clin Inf Dis 2015;60:398) STI clinic: women screened rectally & GU

3055 women screened

Prevalence rectal CT: 12-13%

Rectal scrn: incr detection 44%

25% of rectal-only reported AI

Table 1. Prevalence of Chlamydia Among Women Who Underwent Rectal Screening by Sexually Transmitted Infection Clinic, 20 July–31 December 2012 (N = 3055)

	Calgary		Edmonton	
Anatomical Site	No. Tested	No. Positive (%)	No. Tested	No. Positive (%)
Any site	1570	204 (13.0)	1485	256 (17.2)
Rectal	1570	183 (11.7)	1485	201 (13.5)
Cervix	1500	106 (7.1)	1278	169 (13.2)
Urine	43	4 (9.3)	125	8 (6.4)
	Calgary (n = 191), No. (%)		Edmonton (n = 241), No. (%)	
Chlamydia cases				
Rectal only	89 (46.6)		43 (17.8)	
Genitourinary and rectal	81 (42.4)		143 (59.3)	
Genitourinary only	21 (11.0)		55 (22.8)	

N. gonorrhea: Whom to Screen

Sexually active women < 25 yrs

Other women:

- New or multiple partners
- Prior gonorrhea or other STIs
- Commercial sex workers, illicit drug use
- Living in communities w/ high prevalence

MSM at high risk

(Not MSW)

Possible Causes Recurrent/Persistent NGU

Mycoplasma genitalium: azithro if objective urethritis

? TCN-resistant *Ureaplasma* (inconsistent data)

Trichomonas vaginalis: MSW

- Some ref labs: urine-based *T. vaginalis* NAAT
- NAAT more sensitive than culture
- In high-prevalence areas: presumptive metronidazole 2 g or tinidazole 2 g x 1 after failed 1st-line tx for MSW

HSV

Mycoplasma genitalium in STIs

Cause of male urethritis (sole or co-infx)

- ~20% NGU; ~25% Non-CTU; 30% persistent urethritis

Less definitive cause of female STI

- Found in lower, upper genital tract, often a'sx
- Possible role in cervicitis, PID, pre-term delivery

Diagnosis: no FDA-approved test available

- Suspect: persistent/recurrent urethritis/cerv/PID

Tx: Doxy cure 31%; Azithro cure :85→40%

Moxi 7-14D if failure w/ azithro

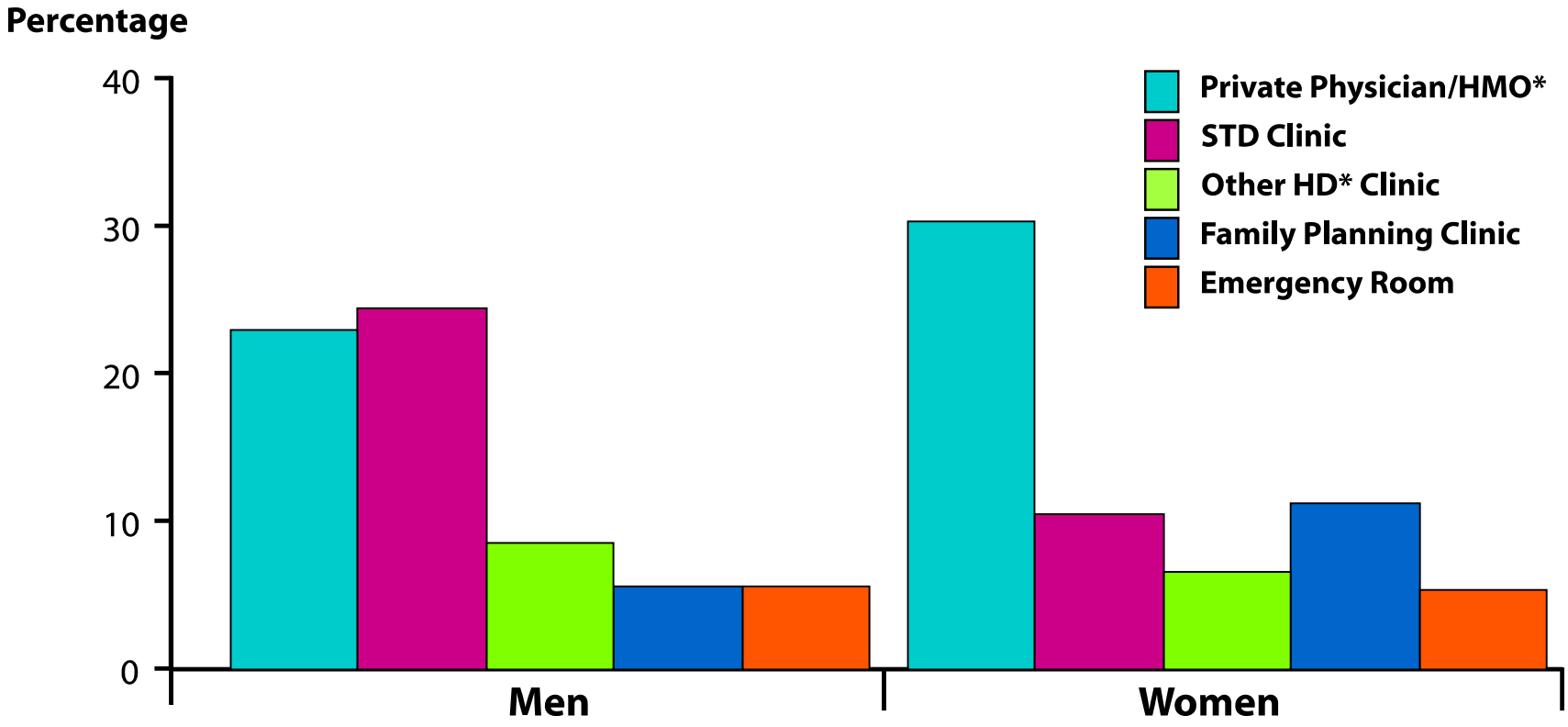
Chlamydia: Evolving Tx

- Doxycycline more effective than azithro

  (NGU per: Sena et al. J Inf Dis 2012;206:357)

  (CDC maintains Azithro or Doxy as 1st line for CT tx)
- Anorectal disease: azithro better than doxy
- Pregnancy: Amoxicillin moved to alternate list (b/c persistent organisms in vitro)

Gonorrhea—Percentage of Reported Cases by Sex and Selected Reporting Sources, United States, 2012



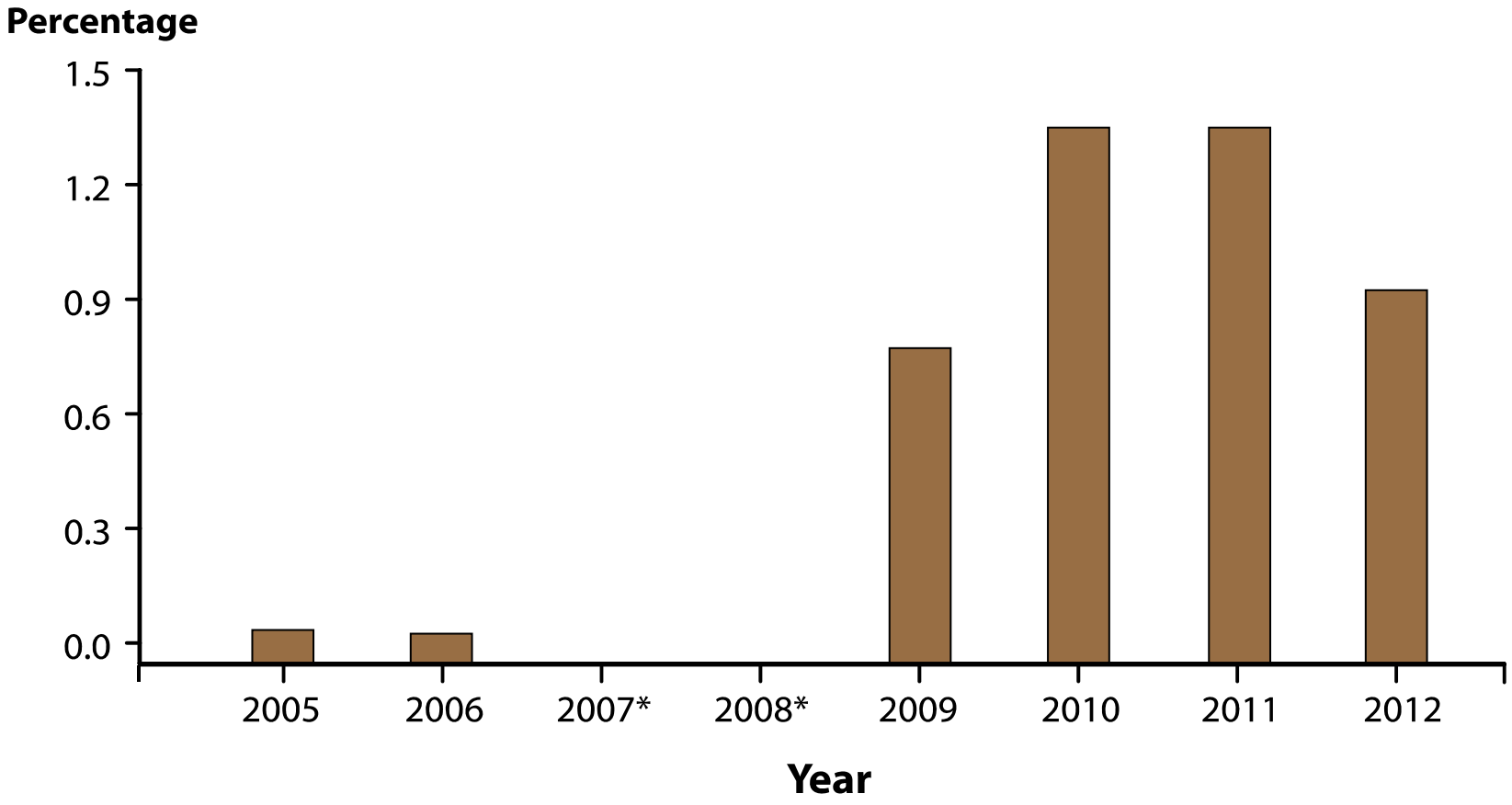
*__HMO__=health maintenance organization; __HD__=health department

NOTE: Of all cases, 11.7% had a missing or unknown reporting source. Among cases with a known reporting source, the categories presented represent 66.2% of cases; 33.8% were reported from sources other than those shown.

GISP: Percent of *Neisseria gonorrhoeae* isolates with resistance or intermediate resistance to ciprofloxacin, 1990–2005

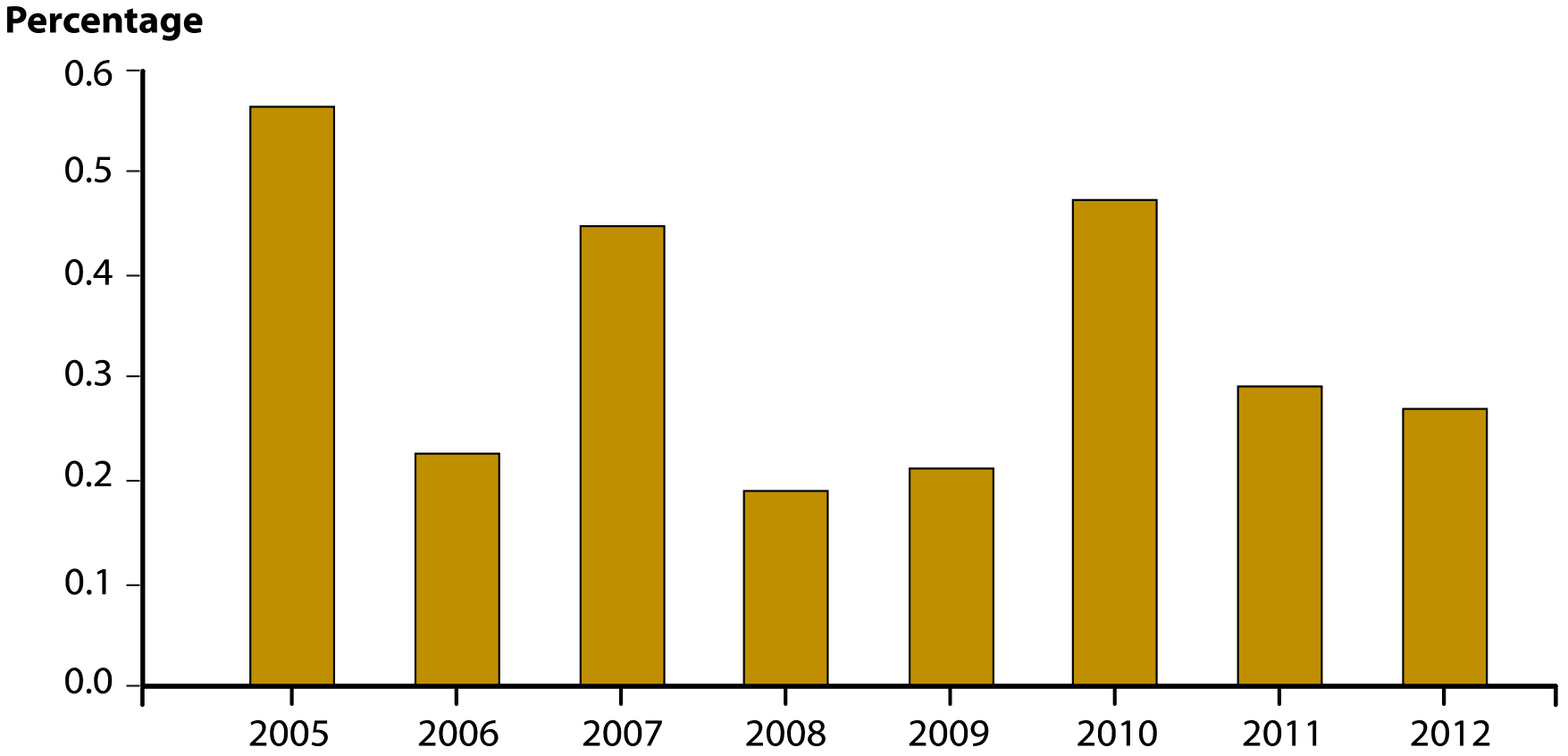
Note: Resistant isolates have ciprofloxacin MICs ≥ 1 µg/ml. Isolates with intermediate resistance have ciprofloxacin MICs of 0.125 - 0.5 µg/ml. Susceptibility to ciprofloxacin was first measured in GISP in 1990.

Percentage of *Neisseria gonorrhoeae* Isolates with Elevated Cefixime Minimum Inhibitory Concentrations (MICs) (≥0.25 µg/ml), Gonococcal Isolate Surveillance Project (GISP), 2005 – 2012

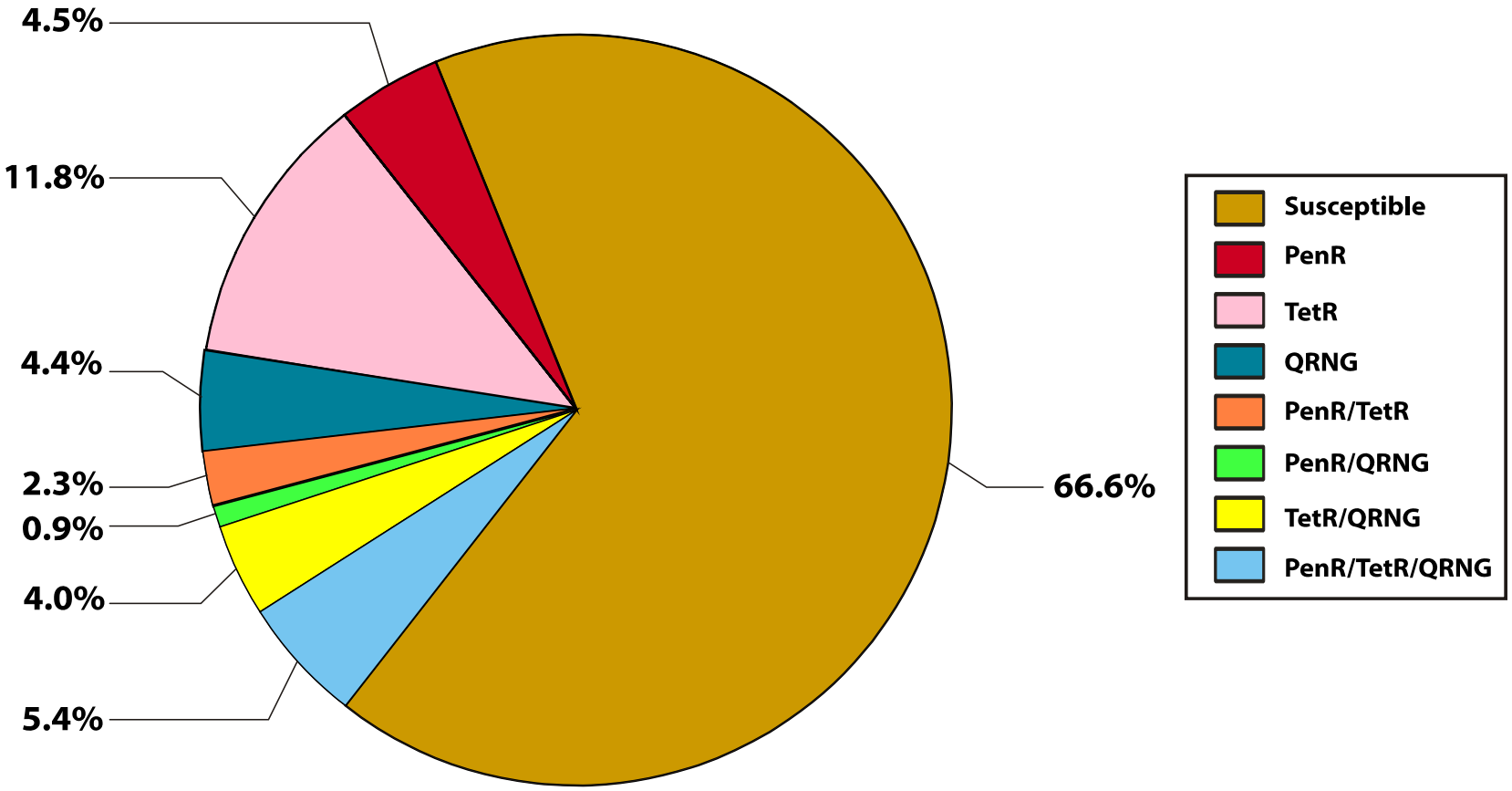


***NOTE:** Isolates were not tested for cefixime susceptibility in 2007 and 2008

Percentage of *Neisseria gonorrhoeae* Isolates with Elevated Azithromycin Minimum Inhibitory Concentrations (MICs) (≥2.0 µg/ml), Gonococcal Isolate Surveillance Project (GISP), 2005 – 2012



Penicillin, Tetracycline, and Ciprofloxacin Resistance Among *Neisseria gonorrhoeae* Isolates, Gonococcal Isolate Surveillance Project (GISP), 2012



NOTE: PenR = penicillinase producing *Neisseria gonorrhoeae* and chromosomally mediated penicillin-resistant *N. gonorrhoeae*; TetR = chromosomally and plasmid mediated tetracycline-resistant *N. gonorrhoeae*; and QRNG = quinolone-resistant *N. gonorrhoeae*.

Gonorrhea Treatment per Revised CDC Guidelines (2013 update of 2010 pub.)

- Ceftriaxone **250 mg** IM **plus**

  Azithro (1 gm) or Doxy** (bid x 7 days)
- Cefixime: no longer 1st-line tx

  If used: perform test-of-cure from site @ 1 wk
- Persistent infection: **culture w/ susceptibilities**
- 2nd line approaches:

  If no ceftriaxone: Cefixime 400 mg + Azithro/Doxy

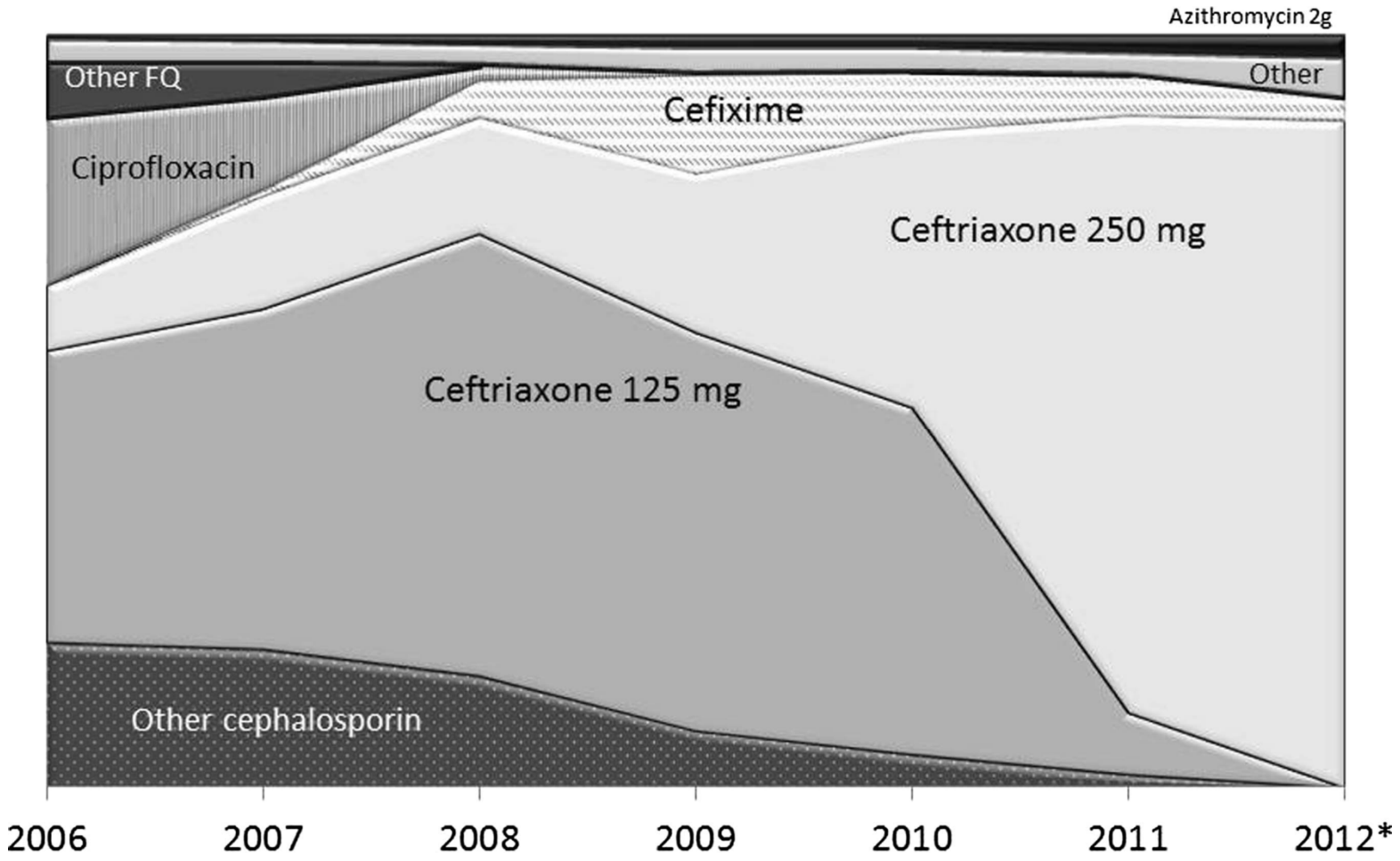
  Severe cephalosporin allergy: Azithro 2 gm**

  Perform **test-of-cure** 1 week (?) after treatment!
- Tx partner w/o office eval: cefixime/azithro
- Stay vigilant for cephalosporin tx failure (cx w/ suscept)

**see proposed 2014 changes

Antibiotics for *N. gonorrhea* in U.S.

(Kirkcaldy Sex Transm Inf 2013;89:iv5-iv10)



2014 CDC Proposals for *N. gonorrhea* Tx

(document seeking public comment)

Ceftriaxone 250 mg IM + azithro 1 gm (std)

If cephalosporin allergy:

- Gent 240 mg IM/azithro 2 gm **or**
- Gemifloxacin 320 mg/azithro 2 gm (~8% vomited)

Doxy no longer a 2nd agent to ceph's

Azithro: mono-tx no longer recommended

If dual tx used: test-of-cure if w/ pharyngeal dz only

Cefix and azithro for partner tx

Take-home points

- Int'l travelers have risk of chikungunya; potential for wider US transmission
- We have conditions for endemic babesiosis
- Transfusion recipients have risk of babesiosis
- Recommendations for screening populations for STIs are changing
- Tx rec's for common STI organisms are changing; causative organisms expanding